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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/644,052	08/19/2003	Arthur M. Krieg	C1037.70048US00	4791

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EXAMINER	
ARCHIE, NINA	
ART UNIT	PAPER NUMBER
1645	
MAIL DATE	DELIVERY MODE
10/29/2009	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/644,052	KRIEG ET AL.	
	Examiner	Art Unit	
	Nina A. Archie	1645	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *13 October 2009*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *100-102 and 104-107* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *100-102 and 104-107* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *10/13/2009*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Continued Examination Under 37 CFR 1.114

1. A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on October 13, 2009 has been entered.

Amendment Entry

2. The amendment filed October 13, 2009 has been entered. Claims 100-102 are amended. Claims 100-102 and 104-107 are currently pending and under examination. Claim 103 has been cancelled.

Information Disclosure Statement

4. The information disclosure statement filed on 10/13/2009 have been considered. An initialed copy are enclosed.

Withdrawal of Objections/Rejections

5. The objection to claims 101 and 102 not disclosing a SEQ ID NO: in the claims is withdrawn and the instant application complies with the requirements of 37 C.F.R. § 1.821-1.825.

6. The rejection of claims 100-104 under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention, has been withdrawn in view of applicants amendments.

Response to Arguments

7. Applicant's arguments with respect to claims 100-102 and 104-107 have been considered but are moot in view of the ground(s) of rejection below.

Claim Rejections Maintained

35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

8. The rejection of claims 100-102 and 104-107 under 35 U.S.C. 103(a) as being unpatentable in view of Krieg et al WO/01/22972A2 April 5, 2001 and Samani et al Antisense and Nucleic Acid Drug Development 2001 Vol. 11 pgs. 129-136 are maintained for the reasons set forth in the previous office action.

Applicant arguments:

Applicants state the Examiner argued that the instant claims are rendered obvious by Krieg et al. because Krieg et al. teach that a chimeric combination of phosphodiester and phosphorothioate oligonucleotide is preferable over a fully modified oligonucleotide, however, this notion is provided in the context of plasmid vectors, that is, cells' ability to take up a plasmid vector containing completely phosphorothioate nucleic acid. Applicant contends that this is taken out of context in the rejection of the instant claims, because the instant invention teaches a chimeric oligonucleotide of up to 40 nucleotides in length and does not pertain to a plasmid vector. Applicants argue there is no disclosure in either cited reference (Krieg et al and Samani et al) concerning specifically sited phosphodiester or phosphodiester-like internucleotide linkages in any immunostimulatory nucleic acid, as claimed in the instant application. Applicants argue the general disclosure in Krieg et al of chimeric backbones does not clearly disclose the instantly claimed specifically sited phosphodiester or phosphodiester-like internucleotide linkages. Applicants argue Samani et al does not provide the skilled artisan any further guidance on selecting the site to place the phosphodiester internucleotide linkage. Applicants argue it would not have been obvious to a skilled person to modify only those particular locations, out of all the possible locations that could be modified, in order to arrive at the instantly claimed invention

because the cited references provide no guidance for selecting the specifically claimed site to place the phosphodiester internucleotide linkage. Applicants argue that the skilled artisan would not have reasonably expect, on the basis of the teachings of the cited references, that such modifications would in fact result in immunostimulatory nucleic acids with improved potency and/or reduced toxicity as compared to fully stabilized immunostimulatory nucleic acids.

Examiner Response to Applicants Arguments:

In response to applicant's statement as set forth supra the claims are specifically drawn to an oligonucleotide having the following structure: 5' T*C_G*T*C_G*T*T*T*T*G*A*C_G*T*T*T*T*G*T*C_G*T*T 3' (SEQ ID NO: 313), wherein * refers to the presence of a stabilized internucleotide linkage, wherein * refers to the presence of a stabilized internucleotide linkage, and wherein _ refers to the presence of a phosphodiester internucleotide linkage and wherein the oligonucleotide has a length of 24-40 nucleotides. Although there is no disclosure in either cited reference (Krieg et al and Samani et al) concerning specifically sited phosphodiester or phosphodiester-like internucleotide linkages in any immunostimulatory nucleic acid. Krieg et al teaches an oligonucleotide comprising the formula N_1-C_G-N_2-C_G-$N_3$3 wherein N_1, N_2, and N_3 are each independently a nucleic acid sequence of 0-20 nucleotides in length and wherein _ indicates an internal phosphodiester internucleotide linkage (see pgs. 2-12, pgs. 18-24, pgs. 27-30, and pg. 34), wherein the immunostimulatory nucleic acid molecule is 4-100 nucleotides long (see pg. 8 lines 8-13). Therefore Krieg et al teach specifically sited phosphodiester or phosphodiester-like internucleotide linkages. Krieg et al teach sequence 343 s wherein s=phosphorothioate linkages which correlates to SEQ ID NO: 313 wherein * refers to the presence of a stabilized internucleotide linkage and wherein the oligonucleotide has a length of 16-40 nucleotides (see table 4 sequence 343 pg. 45). Furthermore, Samani et al teach phosphodiesters are rapidly degraded by serum intracellular nuclease (see Samani et al pg. 129). Therefore one would have been modified at the time the invention was made to place a phosphodiester between the C and the G to produce a oligonucleotide with a CpG that has a phosphodiester internuculeotide linkage and modify the oligonucleotide with stabilized internucleotide linkages such as phosphorothioate as taught by Krieg et al because Krieg et al teach a chimeric combination of phosphodiester and

phosphorothioate oligonucleotide because a cell may have a problem taking up a plasmid vector in the presence of completely phosphorothioate nucleic acid.

As outlined previously, the claims are drawn to an oligonucleotide having the following structure: 5' T*C_G*T*C_G*T*T*T*T*G*A*C_G*T*T*T*T*G*T*C_G*T*T 3' (SEQ ID NO: 313), wherein * refers to the presence of a stabilized internucleotide linkage, wherein * refers to the presence of a stabilized internucleotide linkage, and wherein _ refers to the presence of a phosphodiester internucleotide linkage and wherein the oligonucleotide has a length of 24-40 nucleotides (claim 100), wherein the oligonucleotide consists of 5' T*C_G*T*C_G*T*T*T*T*G*A*C_G*T*T*T*T*G*T*C_G*T*T 3' (SEQ ID NO: 313) (claim 101), wherein the oligonucleotide consist of 5' T*C_G*T*C_G*T*T*T*T*G*A*C_G*T*T*T*T*G*T*C_G*T*T 3' (SEQ ID NO: 313) (claim 102), wherein the stabilized internucleotide linkage is a phosphorothioate internucleotide linkage (claim 104); an oligonucleotide having the following structure: 5' T*C_G*T*C_G*T*T*T*T*G*A*C_G*T*T*T*T*G*T*C_G*T*T 3', wherein * refers to the presence of a stabilized internucleotide linkage, and each _ refers a phosphodiester internucleotide linkage, and wherein the oligonucleotides is 24 nucleotides (claim 105), a pharmaceutical composition comprising an oligonucleotide as defined as an oligonucleotide having the following structure: 5' T*C_G*T*C_G*T*T*T*T*G*A*C_G*T*T*T*T*G*T*C_G*T*T 3' (SEQ ID NO: 313), wherein * refers to the presence of a stabilized internucleotide linkage, wherein * refers to the presence of a stabilized internucleotide linkage, and wherein _ refers to the presence of a phosphodiester internucleotide linkage and wherein the oligonucleotide has a length of 16-40 nucleotides (claim 106); a pharmaceutical composition comprising an oligonucleotide as defined as an oligonucleotide having the following structure: 5' T*C_G*T*C_G*T*T*T*T*G*A*C_G*T*T*T*T*G*T*C_G*T*T 3', wherein * refers to the presence of a stabilized internucleotide linkage, and each _ refers a phosphodiester internucleotide linkage, and wherein the oligonucleotides is 24 nucleotides.

Krieg et al WO01/22972A2 teach sequence 343 s wherein s=phosphorothioate linkages which correlates to SEQ ID NO: 313 wherein * refers to the presence of a stabilized

internucleotide linkage and wherein the oligonucleotide has a length of 16-40 nucleotides (see table 4 sequence 343 pg. 45).

Krieg et al teaches an oligonucleotide comprising N_1-C_G-N_2-C_G-$N_3$3 wherein N_1, N_2, and N_3 are each independently a nucleic acid sequence of 0-20 nucleotides in length and wherein _ indicates an internal phosphodiester internucleotide linkage (see pgs. 2-12, pgs. 18-24, pgs. 27-30, and pg. 34), wherein the immunostimulatory nucleic acid molecule is 4-100 nucleotides long (see pg. 8 lines 8-13). Krieg et al teach a chimeric combination of phosphodiester and phosphorothioate oligonucleotide because a cell may have a problem taking up a plasmid vector in the presence of completely phosphorothioate nucleic acid (see pgs. 36-37).

Krieg et al is relied upon as set forth supra. Although, Krieg et al is silent to teaching a phosphodiester internucleotide linkage between C and G in SEQ ID NO: 313 in an oligonucleotide, formulated in a composition, further comprising a carrier.
Krieg et al teach immunostimulatory nucleotides having a phosphodiester internucleotide linkage are CG. Furthermore, Krieg et al teach nucleic acid that has a phosphodiester backbone linkage the nucleic acid will only have minimal if any effect on the biological activity of the nucleic acid.

Samani et al phosphodiesters are rapidly degraded by serum intracellular nuclease (see Samani et al pg. 129). Krieg et al teach an oligonucleotide formulated in a composition further comprising a carrier (see pg. 7 lines 30-35, pg. 8 lines 1-15, and pg. 10 lines 1-25).

It would have been prima facie obvious at the time the invention was made to place a phosphodiester between the C and the G to produce a oligonucleotide with a CpG that has a phosphodiester internucleotide linkage and modify the oligonucleotide with stabilized internucleotide linkages such as phosphorothioate as taught by Krieg et al because Krieg et al teach a chimeric combination of phosphodiester and phosphorothioate oligonucleotide because a cell may have a problem taking up a plasmid vector in the presence of completely phosphorothioate nucleic acid.

One would have reasonable expectation of success because phosphodiester oligonucleotides with a minimum of phosphorothioate linkages is well known in the art as disclosed by (Samani et al. 2001 Antisense and Nucleic Acid Drug Development Vol. 11 pgs. 129-136).

Conclusion

9. No claims are allowed.

10. Also Examiner notes the omission of the Final Action form paragraph in the previous action dated 6/11/2009, however in the previous office action dated 6/11/2009 the PTOL-326 Form and Public Pair have indicated that the previous office action dated 6/11/2009 is of record as a FINAL action. The Examiner apologizes for any confusion this inadverrtent ommission may have caused.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Nina A. Archie whose telephone number is 571-272-9938. The examiner can normally be reached on Monday-Friday 8:30-5:00p.m.

If attempts to reach the examiner by telephone are unsuccessful, the examiner supervisor, Robert Mondesi can be reached on 571-272-0956. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Nina A Archie
Examiner
GAU 1645
REM 3B31

/Robert A. Zeman/
for Nina Archie, Examiner of Art Unit 1645